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March 1961



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References: 1. Hock, C. W.: *M. Times* 88:320, 1960. 2. McHardy, G.; Browne, D.; McHardy, R.; Bodet, C., and Ward, S.: *Am. J. Gastroenterol.* 24:601, 1955. 3. Robin, B. A.: *Maryland State M.J.*, in press. 4. Farchione, L. A.: *Arch. Pediat.*, Jan. 1961.

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March 1961

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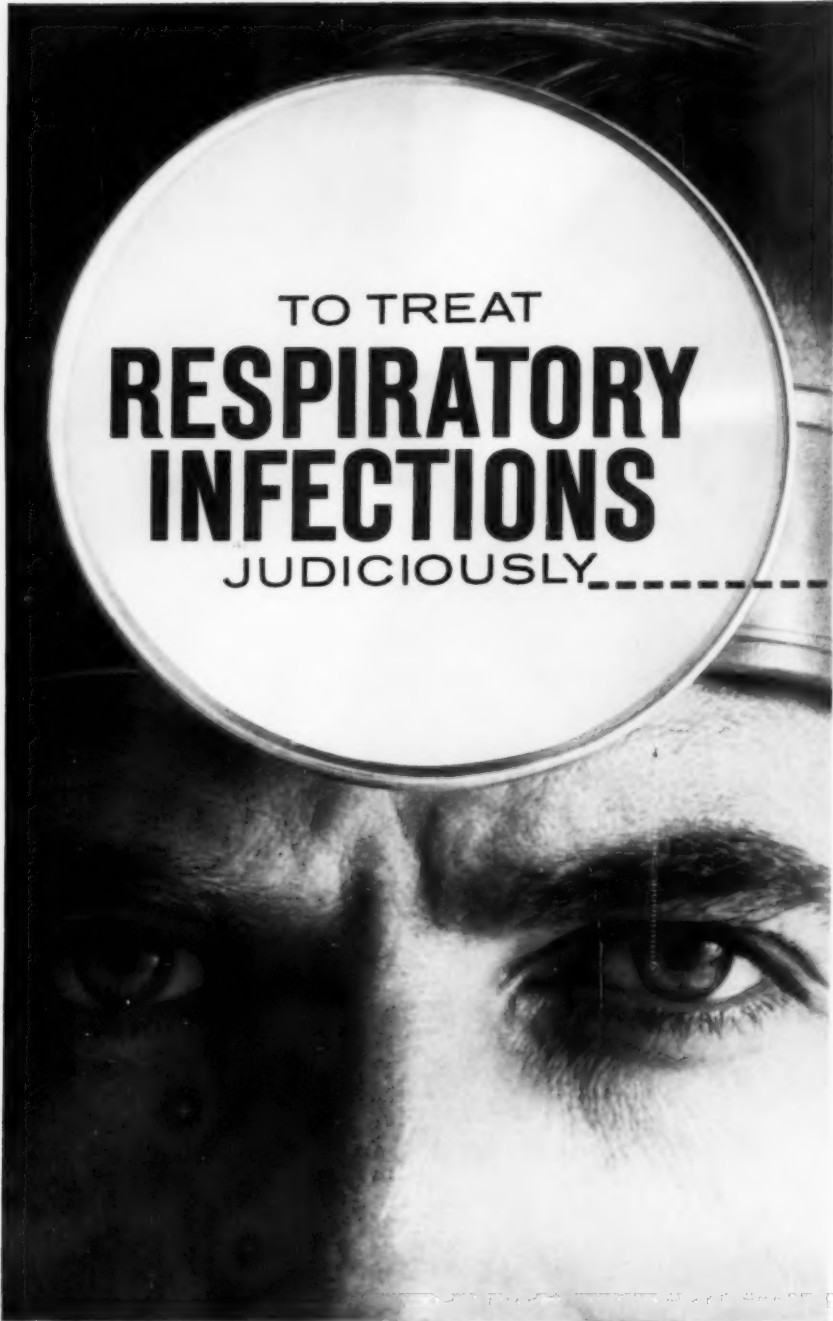
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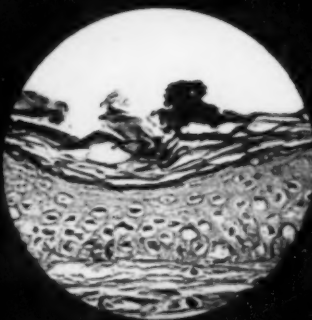
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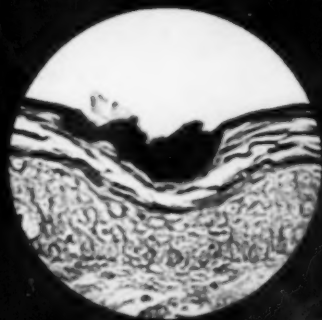
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**References:** 1. Soss, T. L., in *Collect. Letters, Internat. Cor. Soc., Ophthalmologists & Otolaryngologists* 3:177, Dec. 15, 1958.  
2. Budetti, J. A., and Seydell, E. M.: *J. Kansas M. Soc.* 57:59, Feb., 1956.

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## Chromosomal Aberrations

HANS ZELLWEGER, M.D.\*

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JOHN OPITZ, M.D.\*\*

Iowa

IMPROVEMENT of the techniques for the study of chromosomes led to the recognition that the total number of human chromosomes is 46<sup>1</sup> and not 48 as it was taught previously for more than a generation. Man has 22 pairs of autosomal and one pair of sex chromosomes. The autosomes have been numbered 1 to 22 by an International committee of investigators.<sup>2</sup> The autosomes differ in length from 1.5 to 7 micra. They differ as to the position of the centromere or kinetochore. The relative length of the two arms is, therefore, a further differential criterium. The following groups of chromosomes are distinguished: Group A<sup>3</sup> consists of the pairs 1-3, large chromosomes with a median centromere; Group B with the pairs 4-5, large chromosomes with a submedian centromere; Group C with the pairs 6-12, medium sized with a submedian centromere; Group D with the pairs 13-15, medium sized acrocentric chromosomes; Group E with the pairs 16-18 and Group F with the pairs 19-20, both groups consist of short chromosomes with a median or submedian centromere respectively and finally the Group G with the pairs 21-22, very short acrocentric chromosomes. Some chromosomes, for instance 13 and 21 are characterized by satellites, which, however, are not recognized by everybody. The X chromosomes belong as to form and shape to Group C, the Y chromosomes to Group G. (Fig. 1).

The improvement of the methods of examination has indeed stimulated genetic research and led to the discovery of a number of chromosomal aberrations which will be reviewed in this paper. Chromosomal aberrations of clinical interest are non-disjunction, translocation, formation of incomplete chromosomes, polyploidy and mosaics. Some of these chromosomal abnormalities are more or less specific for certain clinical conditions. It is, however, not clear yet, whether or not they cause those clinical conditions. There is however, good evidence of one condition at

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Fig. 1. Karyogram and idiogram of a normal male.

least being definitely caused by its chromosomal abnormality (mongolism).

*Non-disjunction:* During one of the meiotic divisions of an ovocyte or a spermatocyte one chromosome tetrad or diad does not separate but goes in toto to one of the spindle-poles. Thus an abnormal chromosome number results, one telophasic group having 22, the other 24 chromosomes. Consequently, zygotes resulting from such a germ cell with a normal germ cell will have 45 or 47 chromosomes respectively. One chromosome will then be either single or trisomic. The presence of three chromosomes instead of the normal pair in a zygote or in any cell with a diploid set of chromosomes is called trisomy. All the subsequent mitoses will yield a trisomic chromosome in such cases. Non-disjunction may occur in the female as well as in the male gametogenesis. Some evidence indicates that a non-disjunction may occur during cleavage and even later mitotic divisions of the zygote or embryo.

The three most frequently encountered pathologic conditions related to non-disjunction are mongolism, Klinefelter's and Turner's syndrome. In mongolism an anomaly of one of the autosomal chromosomes is found, in the two other conditions the anomaly concerns the sex chromosomes. Trisomy of one of the small acrocentric chromosomes, presumably of the number 21 chromosome is found in mongolism. Mongoloids, therefore, have 47 chromosomes with a triplo 21. This trisomy is by now a well established fact and has been found in a good number of cases. A few exceptions have to be mentioned later on. In Turner's syndrome only one sex chromosome, a single X is found. In Klinefelter's syndrome 3 sex chromosomes, usually two X and one Y, an XXY complement is found. The determination of the true sex may meet with difficulties in some of these and similar conditions. Presence or absence of the sex chromatin bodies in the cells of a buccal smear or a skin biopsy may be of help. The discussion of the sex chromatin, however, is beyond the scope of this paper.

Trisomy of other than the above mentioned chromosomes has been described, though corresponding reports are rather scarce. Patau and Smith and others<sup>7,8</sup> described two conditions of mental retardation associated with different anomalies (see table 1) in which a chromosome of the Group D and E respectively was trisomic. Hayward found a triplo 22 in Sturge-Weber's disease.<sup>9\*</sup> We were able to observe two cases of considerable muscular hypotonia, one with severe, the other with moderate delay in psychomotor development and mongolian features with trisomy of one of the small acrocentric chromosomes of Group G (pair 21 or 22). The differentiation of pair 21 from pair 22 is sometimes not possible. Some authors believe that one pair has satellites, others believe that satellites accompany the chromosomes of both pairs.

Trisomy of autosomes of greater size (Group A and B) has so far not been described. It may be that it is not compatible with life. Fraccaro described a case of trisomy of two chromosome of Group C.<sup>14\*\*</sup> There is on the other hand some evidence that the cases of Sandberg<sup>15</sup> and De Carli<sup>16</sup> with a triplo 6 and 11 respectively may in reality represent cases of trisomy of the X chromosome since the X chromosome belongs with respect to

\*See addendum 1, Page 94.

\*\*See addendum 2, Page 94.

TABLE 1—ABERRATION OF AUTOSOMAL CHROMOSOMES

Total No. of Chromosomes	Translocation Non-disjunction	Sex Chromosomes	Sex Chromatin	Phenotype	Ref.
45	14/18*	XX		Muscular Hypotonia Delay of Psychomotor Development	32
45	1(13)**	XX		Polyspondyly	22
45	15/21	XX		Normal Females in Families with mongolism	23, 24
46	15+2(21)/21	XX XY		Mongoloids	23, 24
46	21+21/21	XY		Mongoloids	10
46	14½21 21+21½21	XX		Mongoloids	33
47	3(6) 2(6)	XX XXX	or ++	Infertile Female with Mental Retardation	15
47	3(11) 2(11)	XX XXX	or ++	Mongolian Features	16
47	3(D)***	XX		Mental Retardation, Convulsions, Harelip, Cleft Palate, Anophthalmia	7
47	3(E)	XX XY		Mental Retardation Mental Retardation (?) Spasticity Micrognathia, Low Set Ears, Congenital Heart, Hernias	8 8
47	3(E)	XX	+	Female, incomplete pterygium disease, congenital heart, hypoplasia of bile ducts	40
47	3(19)	XY		Normal Father of Mongoloid	10
47	3(21)	XX XY		Mongolism	
47	3(G)	XX		Hypotonia, Mongolian Features	34
47	3(22)	XY		Sturge-Weber's Disease	9
48	3(21)	XXY		Klinefelter Mongolism	17, 18
49	3(8) 3(11)	XXY		7 yr. Male, Mental Retardation, Intersex Genitalia, Heart and Kidney Malformation, Mongolian Features	14****
69	3(1-22)	XXY		Male, Mental Retardation, Syndactyly	21

\* Reciprocal translocation

\*\* Fusion of parts of two chromosomes.

\*\*\* 1/2 a trisomy

\*\*\*\* See addendum 2.

size and shape to the Group C as these autosomes do. Both cases had two sex chromatin bodies in their cells which again supports the opinion that these cases represent a trisomy X. (The number of sex chromatin bodies in somatic cells is usually one less than the number of X chromosomes.<sup>41</sup>)

In rare instances, trisomy of more than one chromosome is found. Trisomy of 2 chromosomes raises the total number of chromosomes to 48, as for instance, in two cases where mongolism was combined with signs of Klinefelter's syndrome. The chromosomal analysis revealed a triplo 21 and an XXY complement in both cases.<sup>17,18</sup> Four sex chromosomes, namely XXXY, or XX YY, respectively, have been found in a few additional cases of Klinefelter. Such a chromosomal pattern may be explained by a non-disjunction of either sex chromosome<sup>19,20</sup> in both maternal and paternal germ cells or by non-disjunction of two subsequent meiotic divisions of one germ cell or by non-disjunction of the germ cells of both the mother and the grandmother (secondary non-disjunction). Trisomy of three chromosomes, a triplo 8, triplo 11 and an XXY situation leading to a total number of 49 chromosomes has been described by Fraccaro.<sup>14\*</sup> The patient was a male and displayed mental retardation, heart and kidney malformations, some skeletal anomalies and a few mongolian features. Triploidy of all chromosomes is known to occur in certain animals. So far, only one such case has been reported in man.<sup>21</sup>

One would expect to find an equal number of cases with a low chromosomal count (monosomy) as cases with trisomy. It is surprising but hitherto unexplained why this is not the case. Only a very few cases with 45 chromosomes have been reported. The low chromosomal number was due to an anomaly unrelated to non-disjunction in most if not in all, of the cases (tables 1 & 2).

It is well known that the average age of mothers of mongoloids and Klinefelter's is higher than the average maternal age at birth of normal children. It was difficult to explain this difference though several explanations have been described. In view of the present knowledge it must be assumed that higher maternal age favors the occurrence of non-disjunction. It is interesting to notice that both members of the children with a trisomy of a Group E chromosome were 45 and 46 years of age when they conceived.<sup>8</sup>

\*See addendum 2, Page 94

TABLE 2—ABERRATIONS OF SEX CHROMOSOMES

No. of Chromosomes	Sex Chromosomes	Sex Chromatin	Phenotype	Reference
45	X	—	Turner	
45	X	—	Turner-like	
45	X	—	Intersex-Genitalia	12
46	XX	+	Normal Female	11
46	XX	+	Normal Female	13
46	XX	+	True Hermaphroditism	
46	XY	—	Normal Male	35
46	XY	—	Testicular Feminization	
46	XY	—	Turner-like Female	36
47	XXX	++	Superfemale	37
47	XXX	+ & ++	Female Mental Retardation	38, 39
47	XXY	+	Klinefelter	
48	XXYY	+	Klinefelter	19
48	XXXY	++	Klinefelter	20
48	XXXY	++	Male, Mental Retardation, Webbed Neck, Bone Malformation, Myopia	20
46	XX <sub>1</sub>	+7%	Primary Amenorrhea	28
46	XX <sub>2</sub>		Turner	12

1. One X-Chromosome is partially deleted.

2. One X-Chromosome may be the product of fusion.

TABLE 3—CHROMOSOMAL MOSAICS

Total No. of Chromosomes	Sex Chromosomes	Sex Chromatin	Phenotype	Reference
45/46	XY/X	—	Hermaphroditism	25
45/46	XX/X	+	Turner	26
45/46	XX/X	—	Turner	27
45/47	XXX/X	+ & ++	Turner and Superfemale	28
46/47	XX/XXX		Klinefelter	29
45/46/47 (Transient)			After X-ray treatment	31
46-48	O/Y/YY/YYY/ XX/XXX/XXXX/ XXXXX	+52% ++21% +++9%	Male, Mental Retardation, Microcephaly, Myopia, Hypotonia, Bone malformation	30
48/49	XXXY/XXXXY		Klinefelter	42

**Translocation:** This anomaly consists in the unilateral fusion or reciprocal translocation of a part or a whole chromosome with another chromosome of the same or different pair. Two fused or translocated chromosomes appear then as one chromosome in the karyogram and consequently the total number of chromosomes is reduced by one, or the total number may be normal because on close scrutiny, two abnormal chromosomes may be discerned.<sup>33</sup> In the



Fig. 2. Karyogram and idiogram of a 5 month old boy with muscular hypotonia, slight delay in psychomotor development with 45 chromosomes and translocation.

idiogram of cases with fusion of a whole chromosome, however, an asymmetrical chromosomal pair is found on one place and a single chromosome in another place (See Fig. 2). We were able to study the case of a five month old infant with a slightly delayed psychomotor development and a considerable muscular hypotonia. He had only 45 chromosomes in the karyogram. The idiogram revealed a translocation between a no. 14 and a no. 18 chromosome. Penrose et. al. and Carter et. al. described families of which several female members had only 45 chromosomes. The reduced number was due to a fusion of a no. 15 and no. 21 chromosome resulting in an idiogram AA 15 21 15/21 whereby AA represents the remaining 21 pairs of the chromosomes. It is interesting to notice that a number of mongoloids occurred in both families, though the chance of having more than one mongoloid in a family is about 1 percent only.

How can this be explained? If the idiogram of the ovogonium is AA 15 21 15/21, the following chromosomal patterns can be found in the ova after two meiotic divisions.

A. 15, 21

A. 15/21, 21

A. 15, 15/21

A. 15/21

If fertilization with a normal sperm A, 15, 21 takes place, the probability of a zygote AA 15, 15/21, 21, 21 and hence a trisomy 21 is high. Twenty-five percent of the offsprings have a chance to be mongoloids, although the origin of the triplo 21 constitution in these cases is different from the usual non-disjunction of a chromosome number 21 in other cases of mongolism. This observation today represents the most convincing evidence that the chromosomal aberration is sufficient to produce mongolism independent of environmental conditions. A few other forms of translocation are indicated in Table 1.

*Mosaics*: Some individuals display more than one idiogram. This is called mosaicism. In most instances a mosaic consists of two different chromosomal patterns, exceptionally more than two patterns are found.<sup>30</sup> Most of the presently known mosaics are due to an abnormality of the sex chromosomes (See Table 3). Whether or not a mosaic is due to a non-disjunction during one of the early mitotic divisions is not clear yet.

*Incomplete Chromosomes*: Jacobs<sup>28</sup> described the case of a female with primary amenorrhea, where one of the two X chromosomes appeared hypoplastic as if partially deleted. Interestingly enough, the sex chromatin bodies were found in only 7% of the cells, whereas normal females usually have several times as many cells with sex chromatin bodies.

The perusal of tables 1-3 reveals that several phenotypes can be found with a similar chromosomal pattern and that one and the same phenotype can occur in presence of different chromosomal patterns. This is particularly true for anomalies of the sex chromosomes. A single X, for instance, without another sex chromosome is typical for Turner's syndrome, yet it can be found also in a Turner-like condition with phenotypic masculinization<sup>12</sup> and even in normal females.<sup>11</sup> An XX situation is found in normal females as well as in true hermaphroditism.<sup>13</sup> On the other hand, Klinefelter's syndrome may be associated with an XXY as well as with an XXXY constitution. These and similar observations may indicate that the chromosomal pattern is not the only and exclusive

determinant of the phenotypes. It may well be that chromosomal patterns which appear to be identical at the present time, may reveal differences as better optical techniques become available.

## SUMMARY

The presently known aberrations of autosomal and sex chromosomes are briefly reviewed and a few personal observations are presented.

## ADDENDUM 1

Lehman and Forsman (Lancet 2:1450, 1960) reported two cases of Sturge-Weber disease with 46 chromosomes. We recently studied a two-month old child with convulsions, hemangioma of the right side of the face and the right shoulder, and the typical intracranial calcifications. Thirty-seven cells were counted; thirty-four of them had 46 chromosomes, one probably had 46 chromosomes and two had 45 chromosomes. A normal set of 46 chromosomes also was found in two cases of tuberous sclerosis. 32, 43

## ADDENDUM 2

These authors recently have published a correction (Lancet 2:1303, 1960) based on the finding of multiple sex chromatin bodies. They now postulate an XXXY constitution for this case.

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## **"Bone Chip At-Site" — Skull Homograft in a Child — Preliminary Report**

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**T**HIS exceptional case is reported for a number of reasons. First and foremost is the fact that it is the experience of the authors that in the operative procedure performed in this case of a compound comminuted, depressed skull fracture, bone chip replacement of the type carried out in this patient can be successfully performed when and if it is done within a few hours from the time of the accident. Whether or not the above statement might apply to personnel involved in similar situations on the battlefield, it is not for the authors of this report to say at the present time.

Secondly is the fact that the necessity of subjecting the patient to the trauma of a skull plate insertion, in an instance in which the correction of a depressed fracture unquestionably called for such, was definitely avoided.

The third noteworthy fact which stresses the need for a detailed presentation of this new and at the same time modified procedure, deals with the dangers of infection in many cases of larger bone grafts (be these pegs, fragments, flaps of pedicled or unpedicled variety, and even bone flakes) not excluding those reconstructed at site by diploe wedging, and otherwise.

With the above three main points brought into the limelight, it becomes unnecessary to indulge in fine points and to dwell upon various aspects of complicated techniques, and, least of all upon the chronology of such. The experiences of the authors with military and civilian features of head trauma and the familiarity with the literature involved in such experience over a number of decades, makes them feel that the discussion of special methods dealing with depressed skull fracture in children, is without doubt superfluous, in this presentation. In future publications, and probably in the "final report", the present writers might even express themselves along lines of the necessity of carrying out similar procedures in non-depressed but multiple comminuted fractures and similar cases. This, as well as the topic of the incidence of epilepsy and other complications in "open" versus "closed"

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head injuries, require special attention, as do the incidences of contusion, hematoma, laceration, cicatrization and the vascular disturbances connected with such.

Without further pursuit along clinical signs and symptoms involved in the aforementioned pathological conditions, the writers feel that pediatricians (especially those directing large pediatric services inclusive of pediatric trauma) particularly interested in neuropsychiatric and neurosurgical angles, this is primarily a pediatric (pediatric surgery, that is) problem. Before proceeding with the case as such, so that the pediatrician can profit from this presentation without being burdened with complicated techniques, we will devote a short paragraph to the subject of other approaches, and also refer to standard texts which cover the highlights of skull homografts.

Trauma to the encephalon, even of the "closed head injury" type, is an important factor in the causation of epilepsy according to some outstanding neuropsychiatrists who specialize in seizures. With open head injuries, the sequelae in general, and of epilepsy in particular<sup>1</sup> are greater, especially if the skull fracture is depressed. When the fracture is of the compound category, there is added danger of infection. There is evidently multiplication of complicating features when the area has been repaired and a skull defect remains.

The eventual correction of the defect has been dealt with in so extensive a literature, that it is superfluous for one to indulge in an extensive bibliography concerning such. The insertion of metal plates from silver to tantalum is almost common knowledge to the fund of which the experiences of the last great war was no small contributor. As far as autogenous bone grafts go, there have been many variations. The autogenous grafts, from tibia, rib and iliac bone are the most commonly referred to types. The at-site repair types include the well-known Bagly<sup>2</sup> method, among others. What is highly relevant and rather interesting, is the fact that as late a date as 1946, an authority as outstanding as Barnes Woodhall<sup>3</sup> dealt with the non at-site homograft in a rather complicated multistage fashion.

#### CASE PRESENTATION

R. B. a 9-year-old white male was brought to the hospital in an unconscious state with profuse bleeding from a laceration in

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the right side of the skull and some nasal hemorrhage as well. The admitting physician who found that the cause of the accident was injury by a railroad train, observed that the scalp laceration was deep and that it was probably accompanied by a depressed skull fracture, since the coma was rather deep and the pupils were very sluggish to light.

The patient was checked for lung and abdominal injuries by the admitting doctor who proceeded promptly with X-ray studies of the skull, chest and extremities, paying special attention to the last mentioned since there were abrasions of both knees and legs.

Prior to the moving of the patient to the X-ray pavilion, a lumbar puncture was done. This revealed bloody spinal fluid with an initial pressure of 100 mm of water and the final one of 70 mm of H<sub>2</sub>O, with the patient in the horizontal position. A blood specimen from the finger tip was also submitted to the laboratory.

In the course of taking the X-rays a negative past personal history of the patient was elicited from the parents. The family history was also non-contributory. During the eventual reading of the wet X-ray plates it was found that the rib cage and extremities were negative for fractures but the skull films disclosed multiple fracture lines on the right side, one of these showing evidence of being depressed.

On further checking the patient was found to have a bilaterally positive Babinski, no abdominal rigidity etc., but persistently sluggish pupillary reaction to light. Urine examination was negative. A finger-blood study report disclosed hemoglobin of 10.2 grams and a WBC count of 9,880 with 68% polymorphs, 2% stab forms, 3% Eosinophiles, and 27% lymphocytes.

A summary submitted by the resident surgeon showed that the patient was suffering from a deep 12 cm laceration of the right fronto-parietal region of the scalp, abrasions of both knees and legs and multiple fractures on the right side of the skull, one of which (Figs. 1, 2) was depressed while another extended downwards into the right side of the posterior fossa.

When the Levine tube was put in place and while the stomach contents were emptied, there was some struggling on the part of the patient. It was at this time when it became evident that muscle strength and movements were somewhat diminished in the left upper and lower extremities. Furthermore, during the reflex

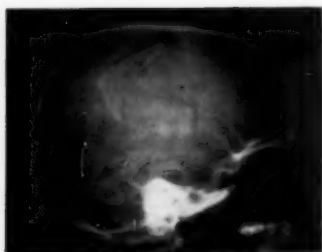


Fig. 1. Right lateral skull roentgenograph of patient R. B., showing multiple fracture lines, one of which extends downwards into the posterior fossa. In the parietal region, the overlapping of the bone gives the commonly known effect characterizing a depressed skull fracture.

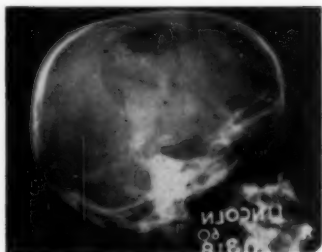


Fig. 3. Right lateral view of skull roentgenograph of patient R. B., showing a defect produced after disposal of the depressed bone fragments. The approximate size and number of the bone chips "at-site" can also be seen spread over the defect.



Fig. 2. Posteroanterior view of skull in patient R. B., age 9 years. In this aspect of the roentgenographic position, the extent of the depression in the skull as well as its actual topography in relation to the superior longitudinal sinus are evident.



Fig. 4. Shows the anteroposterior view of the skull roentgenograph of patient R. B., presenting the findings described in Fig. 3 with the homograft bone chips in situ.

resistance to oropharyngeal manipulation, there was evident a supranuclear paralysis of the left facial musculature. The foregoing especially, but the sluggish pupillary light reflex reactions and the bilaterally positive Babinski toe signs as well, coupled with

the suggestion of some neck rigidity and the deepening coma with which was also associated the shock syndrome complex, all indicated that there was no time to be lost.

Preoperatively an intravenous glucose infusion by means of a cut-down above the left ankle served to combat shock. The infusion also tended to counteract the fluid loss associated with bleeding from soft tissue laceration, maceration, and even avulsion which took place in the right parietotemporal region of the scalp. The comparison between the location of the depressed bone area was evident from the X-ray films and the actual site of the extensive scalp laceration made it evident that a lengthening of the traumatic tear by scalpel incision in order to reach the area of the depressed bone, was unnecessary. It is superfluous to give a detailed description of the types of macerated tissue mixed with galea and bone fragments, other than to emphasize that the shorn-away hairs carried with them actual dirt which had been pressed into the wound. The nature of the surgical procedure which followed, and the choices that had to be made while the major efforts of debridement, release of increased intracranial pressure and osteoplastic and other repairs were instituted, will all become evident from the operative protocol which follows. Besides the increased intracranial pressure to be relieved, there was also the possible necessity that the surgeons might have to deal with brain contusion and cerebral cortex laceration, since the left hemiparesis pointed towards actual damage localized in the left precentral motor cortex. It must be stressed that the last mentioned was located at some distance from the site of the depressed bone nearer to the location of the other simple linear . . . fractures (Fig. 3).

#### OPERATIVE NOTE

Under general anesthesia the area about the wound region was antisepticated, the soft tissues cleansed thoroughly and sterilized as well. There was a 14 cm wound through the scalp, exposing the bone underneath to such an extent that even the galea aponeurotica had also been torn away. Gauze packing was inserted into the lowermost portion of the wound between the scalp (i.e. its inner surface) and the bone itself.

An opening was made into the scalp by means of a perforator followed by a burr from a Hudson drill. From this opening rongeurs were used to elevate and remove the bone fragments which were pressing upon the dura. An area of skull bone  $3\frac{1}{2}$  inches long and a  $1\frac{1}{4}$  inch wide was removed. The pulsating dura

underneath had no tear in it. It was noticed that one of the bone fragments an inch long by half an inch wide was marked by a miniature flock of hair imbedded deeply into the diploe. This was saved for laboratory analysis, since, together with the hair, there was material of a dark earth consistency which had probably been pressed by the traumatic impact deeply into the bone substance situated between the outer and inner osteal layers.

A strenuous effort was made on the part of the senior surgeon to replace 3 of the bone fragments in the course of the attempt to cover up the bone defect. Since there was insufficient bone to be made to span the entire opening, and moreover, since some of the fragments could not be split through the diploe (in younger individuals under similar circumstances, this would be probably much less possible) this effort of replacing the larger bone fragments which were the product of preoperative and operative skull trauma, was abandoned.

In its stead, bone chips averaging three to four cms (Fig. 4), in circumference (about 20 in number) and a few of larger size, were placed in scattered fashion over the dura. The scalp was replaced with stay sutures and penicillin was scattered (this patient was not allergic to penicillin nor to the tetanus antitoxin which he had received) all over and between the bone chips (about one million units in 30 ccs of saline) and onto the dura proper.

The scalp was closed in two layers. For the innermost, curved needles with 0000 silk were used and for the outer, straight needles with 000 silk were employed. Dressings and variety of roller bandages were used and the child left the OR in good condition.

#### POST OPERATIVE COURSE

The following post-operative series of events detailing the variations in temperature changes and other vital signs, laboratory findings and neuropsychiatric features, indicate the general progress as well as the effects of both the trauma and operative events in preventing what might have been a rapidly progressive downgrade cerebral pathologic course.

The temperature varied between 102°F and 103°F from the first to the third post-operative day. From the fourth to seventh day, the temperature remained at 102°F. From the 8th day throughout and to the 15th inclusive, the temperature was 101°F. After that it dropped down to 100°F. The pulse rate was about 110 per minute up to the 7th post-operative day.

It dropped to 100 per minute from the 7th to 15th post-operative day, leveling off to 90 beats per minute after the 15th post-operative

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day. The respiration varied between 30 and 40 per minute for the first few days, and then dropped to 24 per minute around the 7th post-operative day. The blood pressure was 130 mm Hg., systolic over 90 mm diastolic post-operatively till the 7th day; from then on it dropped and remained at 110 mm Hg., and 85 mm Hg., respectively.

Around the operative day when "blood had been given", the Hb value was 10.8 Grams/per 100 ccs and the white blood count was 10,000 cells/per cubic mm with a differential reading of 71% segmented, 28% lymphocytes and one per cent stab forms. On the 4th post-operative day, the hemoglobin value was 8.5 Grams/per 100 ccs of blood and the white count was 8,100 cells per cubic mm. The differential count of the above sample disclosed 82% segmented, and 18% lymphocyte forms. On the 7th day post-operatively the hemoglobin rose to 9.5 grams/per 100 cm of blood. The white blood count dropped to 7,600 cells per cubic mm while the differential of the specimen showed 60% segmented and 40% lymphocytes. Studies of the urine fell within the range of normal.

Other laboratory studies, most of which were made within the first five days post-operatively, involved renal function, the electrolytes and other systemic studies. The  $\text{CO}_2$  volume of the blood was 20%, the blood chlorides value was 109 milliequivalents, the blood Na, 136 milliequivalents and the reading for the K was 5  $\text{mgm}\%$ . Two days post-operatively the urea nitrogen of the blood had a value of 26  $\text{mgm}/\text{per 100 ccs.}$ , and the estimation of glucose was 80  $\text{mgm}/\text{per 100 cubic cms.}$  No sections were taken of the last mentioned tissue specimen; the report merely read "fragment of bone".

Of the post-operative neurological observations the following appear worthy of note. Although the patient was so restless that he had to be kept in restraint, the following signs were observed; there was still a left-sided hemiparesis with a left supranuclear facial weakness, both of which did not become worse post-operatively. The pupillary light re-action was better than that of the preceding day of deep coma, but the left one still reacted more sluggishly than the right. Nystagmus was evident when the eyes were moved to the right. The toe movements on plantar skin stimulation were definitely less. There did not appear to be a reaction in the dorsiflexion of the big toe so that a true Babinski could not be said to be present. The visual fields were intact.

On the second day following the operation the patient was still far too somnolent to cooperate in furnishing detailed clinical neuro-

logical studies. There was definite evidence of diminished movements in the left upper and lower extremities and the left cortical facial paresis still persisted. On the 4th and 5th days subsequent to the operation, the patient was not so restless nor somnolent. Even the suggestion of abnormal plantar skin reactions disappeared, and fundoscopic studies disclosed normal optic disks. It seems that general cooperativeness improved with the progressive effectiveness of the penicillin and streptomycin administrations. The patient cooperated with the changing of the dressings on the 5th and 9th post-operative days. Even on the 10th day following the operative procedure there was still a suggestion of a left supranuclear facial paresis. On the eleventh post-operative day there was still a mild left residual hemiadiadochokinesis. From the above account, it is clear that because of his weakened condition, among other things, the patient was not able to cooperate in finer studies. It is therefore evident that there might have been also some sensory changes in the left upper and lower extremities. However, there was no indication of the clinical neurological signs becoming worse.

There was a gradual evolution in the psychic sphere from somnolence for few days after the operative procedure to moodiness, grouchingness, lack of interest in surroundings, some insomnia later, and even the inability to concentrate attention. These, along with various signs in the left upper extremity, and a mild left supranuclear facial paresis, persisted 2½ months following the accident.

An electroencephalographic study made at this time is described as follows: The general wave patterns consisted of a cycle range of between 6 to 14 waves per second, with an amplitude variation of 10 to 100 microvolts. Anteriorly, there were faster frequencies in the cerebral hemispheres, as against the slower ones of relatively higher amplitude from the posterior portions of the cerebral cortex. The occipital alpha rhythm was present. In general, the pattern was symmetrical and synchronous from all leads. From the bifrontal region there were occasional three per second waves in the 100 to 250 amplitude microvolts category. There was also spiking from these regions, and the latter was strictly confined, at all times to the frontal region. This was necessarily the case with the former. Visual stimulation produced a transitory depression of all potentials. In addition to the above the following are noteworthy findings connected with hyperventilation effects upon the cerebral hemisphere electric patterns of this patient.

Hyperventilation consisted of two periods each with an interval between rest period of three minutes. Long trains of bilaterally syn-

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chronous  $2\frac{1}{2}$  to 3 cps with an amplitude up to 350 microvolts, were seen in all leads. These were sustained even during rest periods.

Summary: The latter findings, especially the slow waves with persistent spikings from the frontal leads were suggestive of a cerebral electrical dysfunction.

#### SUMMARY

The case of a compound comminuted depressed skull fracture in a 9-year-old child is presented. Elevation of the depressed fracture was followed by bone chip replacement of the resulting defect. To date, it is evident that bone chip replacement at site has been successful in this instance of a compound fracture in which the exposure to infection is much greater than otherwise. For success with the procedure, it is stressed that the same be carried out within a few hours from the time of the accident. It is evident this method particularly avoids subjecting the patient to lengthy period of walking around with a skull defect. It also avoids the operative trauma and other features incidental to the replacement of the skull defect by a plate or other artificial means of replacement.

This preliminary case report is offered in detail including positive clinical, roentgenographic, and electroencephalographic findings among other data. The operative technique as well as the post-operative progress of the patient are presented in detail. The authors hope to be able to offer some additional cases as well as the end result of this case later on in a final report dealing with this problem in pediatric neurosurgery.

#### CONCLUSIONS

The case of repair of a compound comminuted depressed skull fracture in a 9-year-old boy is reported. The resulting defect, after the elevation of the depressed bone fragments was filled with the bone taken "at-site". The fragments were formed into small bone chips about 3-5 mm in diameter and 20 in number. No infection or other complications followed the operation. It is emphasized that, to be successful, the procedure must be carried out within a few hours from the time of the accident.

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## **A Comparative Clinical Evaluation of Infants Fed Human Milk, Whole Cow's Milk and Vegetable Fat Milk**

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**I**N general, the American infant has thrived under modern dietary management, whether fed breast milk, cow's milk, evaporated milk or various prepared milk formulas. The infant grows with only minimal symptomatology that can be directly attributed to the nutritional formula. Special cases such as allergy or food intolerance of unknown etiology require changes in diet usually accomplished in a trial and error manner. In many instances, claims for various special foods with particular reference to increased tolerance, digestibility, absorption and decreased gastrointestinal disturbances have been made on the basis of minor differences noted experimentally. These hardly seem justified since clinical confirmation is lacking under normal conditions of infant feeding.

It seemed worthwhile to observe a representative group of infants under normal hospital and home conditions to see whether significant differences in clinical findings could be observed when fed formulas differing both qualitatively and quantitatively in fat content. This opportunity presented itself during the past 3 years while studying the effects of fats on serum lipid changes in infants.

### **METHODS**

The study was composed of four groups of normal, full-term infants fed with various types of milk (Table I).

The hospital oral feedings were withheld for 12 to 72 hours depending on the infant's birth weight. Infants weighing 5 pounds 8 ounces or over received glucose-water feedings for 12 hours, then were placed on a formula. Infants were discharged from the hospital at 3 to 5 days of age. Multivitamin drops were started seven days after the first feeding and by 14 days the

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TABLE I

Average Fat Composition of Feeding (grams per 100 grams)\*\*\*\*

Group	Type of Feeding	Number	Total Sat. Fat	Palmitic	Stearic	Total Unsat. Fat	Oleic	Linoleic	Others	Iodine No.
I	Breast Fed	66	46.0	22.0	7.0	48.0	34.0	trace	7.0	63
II	Evaporated Milk* Formula	93	59.1			40.9				
III	Whole Milk** Formula	68	55.0	25.0	12.0	39.0	33.0	3.0	2.0	25-42
IV	Prepared Milk*** Formula	70	44.8	17.4	10.8	55.9	38.3	14.4	0.9	58-59

\*1:2 dilution with added dextri-maltose

\*\*2:1 dilution with added dextri-maltose

\*\*\*Diluted 1:1 - 20 cal./oz.

\*\*\*\*Home Economics Research Report No. 7, U. S. Department of Agriculture

infants were receiving 0.6 cc. daily. Supplementary foods such as cereals, fruits, vegetables, etc. were permitted at approximately three months of age.

The infants were seen for monthly follow-up visits in the Well Baby Clinic when weight and length were recorded. A complete physical examination was performed and blood specimens obtained. At these visits interval histories were obtained with particular reference to regurgitation, vomiting, diarrhea, constipation, skin rashes and other side effects.

#### RESULTS

In a comparison of the four groups of infants, only minimal differences were observed (Table II).

Growth as measured by weight gain per week and linear growth per month were substantially the same in all groups (Table II). The difference in weight gain favoring evaporated milk in comparison with other feedings is not statistically significant.

TABLE II

<i>Grp. No.</i>	<i>Avg. Wt. Gain Oz./wk.</i>	<i>Avg. Length Gain In./mo.</i>	<i>Regurgitation</i>	<i>Vomiting</i>	<i>Diarrhea</i>	<i>Constipation</i>	<i>Rashes</i>	<i>Peri-anal Dermatitis</i>
I Breast Fed (66)	6.0	1.5	0	0	1	0	0	0
II Evap. Milk (93)	7.0	1.5	1	1	4	2	7	0
III Whole Milk (68)	6.0	1.5	4	2	2	2	4	5
IV Prepared Milk Formula (70)	6-1/3	1.5	0	1	1	0	1	0

Note: All gastrointestinal symptoms and skin manifestations were minor and cleared spontaneously despite continuation of the particular feeding.

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There are slight apparent differences between the various groups studied with respect to the incidence of regurgitation, vomiting, diarrhea and constipation. It might appear that whole milk and evaporated milk formulas are the chief offenders. However, it should be noted that these symptoms were only transient and cleared up spontaneously while the infants continued on the same feeding.

Rashes also appear more frequently in the evaporated milk and whole milk groups. In the evaporated milk group, three were diagnosed as "heat rash" and two as seborrheic dermatitis. All cleared by the time of the next monthly clinic visit.

#### DISCUSSION

This data indicates that all infants did well on their respective feedings. Normal weight and length increments were present in all series. The infants of all groups were normal in every respect, except for the usual occurrence of transient regurgitation, vomiting, and rashes. There is no indication that butterfat was less well tolerated or absorbed than a corresponding vegetable fat formula.

A link has however been demonstrated between vegetable fats (i.e. essential fatty acids) and cholesterolemia. These findings have been extended to include the demonstration of an hypocholesteremic effect in infants when fed a formula high in essential fatty acids. Some authors have attempted to link these effects on blood lipids to atherogenesis. Mann<sup>1</sup> has given the most logical discussion which makes clear the lack of significant data and the need for further experimental studies. It has even been suggested experimentally that corn-oil-fed rats reacted more unfavorably in glucose tolerance response in alloxanized animals than in those fed saturated fats.<sup>2</sup>

The essential fatty acids are found abundantly in nature, are readily obtained and usually consumed in fairly large quantities. Judicious food selection easily provides adequate amounts of polyunsaturated fats (EFA). It is difficult to believe that a deficiency of EFA exists in the American diet. It has been suggested that a specific ratio of saturated to unsaturated fat is required. This relationship has not as yet been demonstrated. The presence of modest differences in the ratio of saturated fat to EFA in various milk formulas provides no evidence in favor of one or the other.

## SUMMARY

1. 297 infants were studied for six months on an outpatient basis to determine possible differences between breast feeding, evaporated milk, whole cow's milk and vegetable fat formulas with respect to fat tolerance, absorption, utilization and gastrointestinal disturbances.
2. Weight gains and length increments were essentially the same in all groups.
3. The incidence of regurgitation, vomiting, diarrhea and constipation was not significantly different in any of the four groups. Minor symptoms cleared spontaneously while on the same feedings.
4. Rashes and perianal dermatitis, slightly higher in the cow's milk group, were found to be heat rashes and seborrheic dermatitis which cleared spontaneously and were not specifically related to the feeding.
5. On the basis of these findings, there is no clinical evidence of superiority of one type of fat over another with respect to the measurements used.

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## The Role of Moniliasis in Diarrhea of Marasmic Infants — A Controlled Study of Nystatin

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### PART II

IN another article<sup>1</sup> the high incidence of candidas in the stools of marasmic infants with diarrhea was asserted. The significance of the presence of the fungus in the stools and the problem of the diagnosis of intestinal moniliasis were discussed.

While realizing that gastroenteritis in undernourished infants is of multiple etiology, it was thought that in cases with a high degree of intestinal infestation with candidas, a controlled therapeutic trial of a very specific antimonilial agent like Nystatin might be a useful procedure in assessing the significance of such infestation.

#### MATERIALS AND METHODS

Undernourished infants 1-12 months, suffering from diarrhea were investigated during the period of May to August, 1960. Excluded were cases of frank dysentery or of proved *Shigella*, *Salmonella*, enteropathogenic *Escherichia Coli*, Amoebic or Lambliar infections, and also cases of severe parenteric infections. Cases admitted for therapeutic assay were chosen according to either of the following criteria:

- 1—The occurrence of monilial lesions in the mouth or skin provided the stools yielded a "profuse" growth of *Candida* on culture.
- 2—Colonization of the gut by *Candida* as evidenced by the presence of hyphae and chlamydospores in the stools when examined microscopically, even in absence of clinical evidence of moniliasis.

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According to the severity of diarrhea, cases were assessed after admission as "mild" or "severe". Successive cases of the same severity were allocated in rotation to either the "trial group" receiving Nystatin, or the "control group" receiving Sulphaguanidine. There were thus four severity-treatment groups.

A Nystatin suspension, Mycostatin "Squibb", was used in an initial dose of 600,000 units daily until the stools were negative, then half this dose was given daily for the rest of 6 to 10 days. A trial of 300,000 U. initially in 3 other mild cases and of 800,000 units daily in 2 severe cases was also practiced. Trial or control cases markedly deteriorating under such chemotherapy were given in addition Streptomycin or Chloramphenicol by mouth. The usual fluid and electrolyte therapy, dietetic, symptomatic and supportive treatment was undertaken. Penicillin was administered to all, and intramuscular Streptomycin to a few cases, to control parenteric infections.

Rectal swabs (with a glass sheath) were taken: before admission, on the third day of treatment, once or twice more before discharge, and at an average period of 8 days after discharge. Also swabs from the mouth were taken from all cases with oral thrush; and skin swabs moistened with Sabouraud broth were obtained from diaper thrush lesions after washing the area with soap and water. Blood culture for *Candida* was performed for most cases on admission. Blood picture and urinalysis were undertaken in all cases; urine culture, blood culture for *Salmonella* and Widal reaction in suspicious cases.

The progress of cases was recorded every week-day by the same observer; stools, body-weight and temperature were charted, and mouth and diaper thrush lesions observed.

For comparative purposes 30 bacteriologic controls of nearly the same age group as the cases, but of normal weight and not suffering from diarrhea or thrush, were chosen for stool examination for *Candida*.

*Bacteriologic techniques*:—A loopful of fresh and fluid stools emulsified in a drop of saline were examined microscopically for the presence of yeast-like cells or mycelial hyphae. The rectal swab (R.S.) was then smear-planted over half a plate of Littman's oxgall-agar treated with Streptomycin (40 units per ml of the medium). Incubated at R.T. (30°-35°C), 3 days on the

average were necessary before isolate yeast-like colonies could be recognized, fished and transplanted to Sabouraud's agar. Single colonies growing thereon were then inoculated on slants of the same medium and identified morphologically. Skin and mouth swabs were grown on Sabouraud glucose-agar; blood culture on fluid Sabouraud.

*Toxonomic classification*:—The ecologic classification and identification of *Candida*<sup>2</sup> comprised a systematic study involving: the morphology, the mode of reproduction and the formation of blastospores and chlamydo-spores on corn-meal agar slide culture; the characters of the growth on fluid Sabouraud; Fermentation reactions of the main sugars; auxanographic study of sugars utilization; agglutination tests using *C. albicans* antiserum and finally pathogenicity tests by I.V. inoculation into rabbits.

*Profuseness of the Candida population in stools*:—A preliminary assessment was made by the direct microscopic examination of saline emulsion of the fresh stools. The presence of one or more yeast-like cells per H.P.F. ( $\times 450$ ) was considered profuse. Also it was estimated according to its growth on Littman's oxgall-agar (50 colonies or more being considered *profuse*, 10-50 *moderate* and less than 10 *scanty*). In the latter part of the work, however, actual enumeration of the yeast population in each rectal sample was undertaken by the pour plate count culture<sup>3</sup> using Waksman's agar medium<sup>4</sup> acidified with  $N/1$ ,  $H_2$ ,  $SO_4$ , and the results were read after 24 hours only at R.T.

#### RESULTS

*Bacteriologic diagnosis of Admission rectal samples*:—By direct microscopic examination of R.S. it was possible to identify *Candida* in 16 (53.33%) of the 30 admitted cases. In 10 such cases a presumptive diagnosis was made on account of the presence in the stools of yeast-like cells with or without spores. In the remaining 6 cases, however, branching mycelial hyphae with clusters of blastospores and occasionally with terminal chlamydo-spores as well as yeast cells were present in the same preparation. This is taken as evidence of colonization of candida in the gut. By culture of R.S. on Littman's agar, the growth was profuse in 29 cases and moderate in only 1 case. The significance of such profuseness was substantiated by actual enumeration of candida in the stools. For this purpose the stools of 14 cases in the group were cultivated in parallel both on Littman-oxgall as well as on Waksman. On the former

TABLE I

Distribution of *Candida* in Stools, Mouth and Skin  
of 30 cases of Intestinal Moniliasis.

Species	Number of positive isolations from			Total
	Stools	Mouth	Skin	
<i>C. albicans</i>	11	10	2	23
<i>C. stellatoidea</i>	10(3) <sup>δ</sup>	3	0	13
<i>C. tropicalis</i>	12	8	5	25
<i>C. Guilliermondii</i>	0	0	1	1
Total:	33	21	8	62

δ 2 species isolated together : *albicans* on one  
and *tropicalis* on 2 occasions.

medium, the growth of *candida* was "profuse" in all the cases whereas on Waksman's agar the *candida* population varied greatly and ranged from  $10^5$  to more than  $10^6$  cells per ml. of fresh fluid motion. Such high counts had a still greater significance when they were compared with those that were made on the stools of 11 healthy infants that had been positive for *candida* (Table 2). Diarrheal stools yielded very high counts (over  $10^6$  cells per ml.) in 8 (57%) and over  $10^5$  cells per ml. in 3 (21.4%) more cases. Whereas

TABLE II

Comparison of the cell counts in the stools  
of healthy and diarrheal infants.

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Species	Concentration of yeast cells per ml. of stools									
	10 <sup>4</sup> to 10 <sup>5</sup>		10 <sup>3</sup> to 10 <sup>4</sup>		10 <sup>5</sup> to 10 <sup>6</sup>		> to 10 <sup>6</sup>		TOTAL	
	C.	G.E.	C.	G.E.	C.	G.E.	C.	G.E.	C.	G.E.
<i>C. albicans</i>	2	-	1	-	1	-	-	2	4	2
<i>C. stellatoidea</i>	1	-	1	2	1	2	-	3	3	7
<i>C. tropicalis</i>	1	-	2	1	1	1	-	3	4	5
TOTAL:	4	-	4	3	3	3	-	8	11	14

C = controls (healthy children)  
G.E. = gastroenteritis.

formed stools from the 11 controls yielded low counts (less than  $10^5$ ) in 8 (72.7%) and none a count of over  $10^6$  cells. In the 19 other controls of healthy infants R.S. yielded no growth of candida at all. It could be inferred therefore that a count of  $10^5$  -  $10^6$  cells per ml. is a safe threshold for normal controls and that higher counts is a feature that characterizes diarrheal stools that are associated with species of candida.

*Distribution of species of Candida:*—From the 30 cases of GE that were positive for candida, 62 isolates were made from various sites (stools, mouth and skin). These were distributed as follows: *C. albicans* 23, *C. stellatoidea* 13, *C. tropicalis* 25, and *C. Guilliermondii* 1, (table 1). Apparently *C. tropicalis* was more frequent than the other species. However, if *C. stellatoidea*, a species variant<sup>5</sup> of *C. albicans*, is added to isolates of the latter species then *C. albicans* predominates and accounts for 36 (58%) of all the candidas in the series. The distribution of *C. albicans* was also significant, for contrary to expectations and despite evident clinical lesions it was more frequent (21 isolates) in the stools than either in the mouth (13) or the skin (2 isolates). Many contest the role of Candida in the stools simply because it may be a normal inhabitant of the mouth and the parasite is then considered as an intestinal transient. An attempt was made therefore to compare the species isolated from the mouth with those that were recovered from the stools of the same patient in a group of 24 cases. Complete correspondence of the mouth and stools species occurred in 18 cases; whereas in the remaining 6 cases, the species from the rectum were different from those that were recovered from the mouth in 3, while no Candida was present in the mouth of the remaining 3 cases.

#### RESULTS OF TREATMENT

All 30 cases were admitted, each for a period of 8 - 14 days. Sixteen were trial cases and 14 were controls.

Table 3 sums up the clinical data and shows that the trial cases were comparable with the controls in their initial condition, as well as in the antimicrobial therapy they received in addition to Penicillin. In this connection it may be mentioned that none of the cases receiving the former therapy whether parenterally or orally showed a favorable progress.

The results of treatment (table 4) show that the progress of the mild cases receiving Nystatin was definitely superior to controls of comparable severity. Thus of 9 trial cases, 3 recovered completely

TABLE III

Comparison of clinical condition and factors possibly influencing Nystatin-treated cases and controls.

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	<u>Nystatin</u>	<u>Controls</u>
Total No. of cases	16	14
Age less than 6 months	9	6
No. of severe cases	7	6
No. of cases in first degree of marasmus	4	2
" " " " 2nd " " "	7	8
" " " " 3rd " " "	5	4
" " " with chronic diarrhea	13	12
" " " with oral thrush lesions <sup>§</sup>	12	14
" " " " diaper " " <sup>§</sup>	5	7
" " " " parenteric infections <sup>+</sup>	13	13
" " " of other antibiotics <sup>++</sup>	4	4

§ Whether present before or appearing after admission; some cases had both types of thrush.

+ Most were U.R.I. and/or bronchitis, Otitis media was present in 2 controls and gluteal abscess in one trial case.

++ In addition to Penicillin - See Text.

in less than 2 weeks, 3 showed early marked improvement, 3 improved slightly, and none died. Remarkable was that case 13, an infant in the third degree of marasmus showing colonization of *C. albicans* in the gut despite the absence of any clinical evidence of moniliasis, recovered in less than one week and remained well thereafter. Whereas of the 8 control cases only one showed an early improvement, non recovered completely, and 2 died. On the other hand, severe cases showed no marked difference in progress between the trial and control cases. Although their stools were free from other organisms of definite pathogenicity, yet they presented with the clinical picture of an acute episode of 'infective gastroenteritis'. Relapses of diarrhea occurring during treatment were more common in the trial than in the control cases, their num-

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ber being 6 and 2 respectively. Those in the trial cases were mild, occurred early in treatment and subsided rapidly on reducing the dose of Nystatin. They should be thus considered as a side-effect of the drug. Moreover, vomiting of the drug occurred in one case.

TABLE IV  
Comparison of Progress of Nystatin-treated  
cases (N) with that of controls (E)

	Mild		Severe	
	N	E	N	E
Total No. of cases	9	8	7	6
No. of cases making a clinical recovery $\delta$ in $< 14$ days	3	0	2	0
No. of cases improving in $< 7$ days $\delta\delta$	3	1	1	2
No. of cases with no or slight improvement on discharge	3	5	0	2
No. of deaths	0	2	4	2(+1)*

$\delta$  This entails normal stools for at least 3 days successive days, adequate gain in weight, good appetite and improved general condition.

$\delta\delta$  Cases making a clinical recovery are not included in this assessment.

+ Died one day after discharge

On the other hand, of 7 trial cases followed up after discharge, 3 relapsed both clinically and bacteriologically, whereas 3 out of 5 controls had a relapse of diarrhea. All mouth lesions cleared after Nystatin. Skin lesions also recovered or improved greatly. Whereas in controls new skin lesions often appeared or increased, and in a few cases oral thrush developed after admission.

*Bacteriologic findings correlated with the clinical results:*—Table 5 shows the intensity of infestation in the trial cases and in the therapeutic controls before treatment; it so happened to be comparable in the 2 groups. Case No. 38, a control, yielded only a "moderate" growth of *Candida* from the stools; however it was included in the therapeutic assessment because it had lesions of thrush of the mouth

and skin. Moreover, its initial "moderate" growth became "profuse" after treatment. This was possibly related to the antimicrobial agents used in addition to Penicillin.

Excluding 1 case where gentian violet was applied to the mouth against advice, the intensity of growth of candida remained the same in all but one control, where it diminished after treatment. On the other hand, all trial cases became negative or yielded a "scanty" growth of candida after 3-4 days of treatment (table 5). After cessation of Nystatin, however, 5 out of 7 followed-up cases became positive, but no clinical relapse was observed in 2 cases reported to have a profuse growth of candida on Littman's medium; in one of the latter this bacteriological relapse occurred as early as 2 days after the end of Nystatin.

TABLE V  
Bacteriologic findings in rectal swabs before  
and after treatment.

	Trial Cases		Controls	
	Before treat.	After treat.	Before treat.	After treat.
Total No. of cases examined	16	13 <sup>#</sup>	14	12 <sup>##</sup>
Cases showing colonization on direct microscopic examination.	2	0	4	0
Cases with profuse culture of candidas	16	0	13	10
Cases with moderate culture of candidas	0	0	1	1
Cases with Negative or scanty growth	0	13	0	1 <sup>##</sup>
Cases with Positive blood culture	1		1	

<sup>#</sup> The number of cases is less than the original because of the cases dying early after treatment.

<sup>##</sup> One control became negative after use of gentian violet to mouth against advice.

Two cases (28, 44) had positive blood cultures for *C. tropicalis*. They were in the second degree of marasmus, in bad general condition, and had chronic diarrhea of some severity. Case 28 had oral thrush, and evidence of colonization of candida in the gut. After an initial improvement on non-specific treatment, it had a severe re-

lapse of diarrhea, 2 weeks after discharge, during which *C. albicans* and *S. flexneri* were grown from the stools. Whereas case 44, with a recent history of bacal and diaper thrush, had no evidence of colonization of *Candida* in the gut, but its stools yielded a profuse growth of *C. albicans*, that disappeared 7 days after treatment with Nystatin, concomitant with recovery from diarrhea.

#### DISCUSSION

Moniliasis is one of the conditions where infection and disease are different. This is, in part, because much depends upon the host-parasite balance, and partly also because of the lack of well-defined criteria for the diagnosis of deep-seated thrush. This was stated by a B.M.J. annotator (1950) to be a matter of conjecture.<sup>6</sup> Again fatalities due to *C. albicans* are not always recognized.<sup>7</sup> The intestinal lesions in children may be minute and easily overlooked,<sup>8</sup> being recognized only by histological examination.<sup>6,9</sup> Even then, the pathological lesions of intestinal moniliasis are known to be very uncommon.<sup>6,12</sup> The discrepancy between this pathological incidence and the clinical impression based on the tendency to vomiting and diarrhea in infants with thrush<sup>10</sup> needs further investigation. In fact there are yet only few convincing reports on the etiological relation of candidas to infantile diarrhea. Some of these reports<sup>11,13</sup> depended on the isolation of candidas from the stools; but in only two<sup>11,14</sup> did the authors state the bacteriologic evidence for the diagnosis of intestinal moniliasis, apart from the mere presence of candidas in the stools. In all but one,<sup>11,12,13,15</sup> such evidence was corroborated with clinical, and in two<sup>11,15</sup> reports with bacteriologic recovery also, after the use of an antimonilial agent. However, no one used therapeutic controls for assessment of clinical and bacteriologic recovery.

Admittedly, one of the definitive procedures, perhaps the most definitive,<sup>16</sup> to establish moniliasis as the cause of gastrointestinal symptoms, is the use of the therapeutic test. In the present work this was applied on a controlled trial basis. Though the trial cases receiving Nystatin were clinically and bacteriologically comparable with the controls receiving sulphaguanidine, the mild cases in the trial group progressed much more favorably than those in the control group. Whereas severe cases in either group showed no marked difference in progress. This is contrary to the results obtained in a controlled trial with chloramphenicol in a previous work,<sup>17</sup> mild marasmic cases did not benefit so much as severe cases. Hence in severe cases, which presented clinically as "acute infective

gastroenteritis", candida probably did not play the main role in diarrhea; possibly other unidentified factors were responsible. However, the role of candida in the mild but often intractable diarrhea of marasmic infants, especially those in the third degree of marasmus, is obvious, and the progress of case<sup>13</sup> on specific treatment is impressive. Though the effect of Nystatin was not expected to be permanent under conditions of severe debility, yet a follow-up of the cases showed relapses to be less common in trial cases than in controls. Bacteriological relapses, however, were not necessarily accompanied by clinical relapses in the trial cases, an observation previously made by Blank.<sup>16</sup> In this respect, it should be pointed out, however, that in most bacteriologic relapses, the candida counts in the stools were of the order of  $10^5$  -  $10^6$  cells per ml. which is proposed to represent the threshold of normal counts.

The concomitant disappearance of candida on clinical recovery of the trial cases, and its persistence in the same intensity in all but one controls lends further support to the significance of this fungus in the stools of the cases under study.

Of the side-effects of Nystatin, mild and transient relapses of diarrhea seemed to be common, and mild vomiting occurred in one case. Similar side-effects have been noted by other workers.<sup>18,19</sup> They subsided on diminishing the initial dosage. It may be added that though the usual initial daily dosage was 600,000 units, a dosage of 300,000 units was enough to produce a negative culture in 3 mild cases. However, an initial dosage of 600,000 units daily to be halved as soon as a negative culture is obtained seems to be a safer procedure.

From the foregoing it is emphasized that the intractable diarrhea commonly seen in marasmic infants should receive more than a passing interest; nor should such cases be dismissed with an intestinal chamotherapeutic drug and an acid milk after a routine examination of the stools, urine etc. . . . Although a profuse growth of pathogenic candidas from the stools is compatible with health, yet in marasmic infants where superficial thrush lesions are common, such bacteriologic evidence of intestinal infestation should be sought; and the diagnosis of intestinal moniliasis confirmed by the use of an antimonilial agent.

#### SUMMARY

A controlled trial was undertaken with Nystatin in 30 cases of diarrhea in marasmic infants, assessed to be suffering from intes-

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tinal moniliasis on both clinical and bacteriologic grounds, for the purpose of establishing the cause-effect relationship in this condition in marasmic infants. Mild but chronic or even intractable cases of diarrhea definitely benefited as compared with the controls, whereas severe cases did not. These results are correlated with both the bacteriological results before and after treatment, and also with the clinical picture of gastroenteritis. A plea is made for being "moniliasis conscious" in dealing with diarrhea in marasmic infants. A timely use of an antimonilial agent would confirm the diagnosis, and turn the balance in favor of the host.

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## Poison Control . . .

### POTASSIUM PERMANGANATE POISONING

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**D**URING 1960, 42 incidents of potassium permanganate poisoning were reported to the New York City Poison Control Center. Twenty-two of these incidents occurred in individuals under 20 years of age. The age and sex distribution is as follows:

Age	Male	Female	Total
Under 2 years	2	3	5
2 years	7	3	10
3 years	1	2	3
4 years	1	1	2
5 years	—	1	1
6 years	—	1	1
Total	11	11	22

All the incidents reported to the Center during 1960 were happily nonfatal. The most common symptoms in the cases reported to the Center were burning in the mouth and throat and vomiting, but many of them were asymptomatic.

In the adults, some ingested potassium permanganate with suicidal intent. There have also been several cases of uterine bleeding resulting from the misuse of this product in an attempt

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to induce abortion. In one of these cases in which the patient needed a transfusion, she refused it on the basis of religious beliefs, a point of view which apparently did not apply to the original use.

As indicated in a previous publication,<sup>1</sup> the Director of Obstetrics of a large New York City hospital requested that the Department ban the sale of this drug over-the-counter since often women inserted potassium permanganate pills sold by pharmacists without a prescription and as a result suffered from burns and severe vaginal bleeding. Many such patients, when admitted to the hospital, are also in shock, requiring several transfusions; some develop disfiguring scars leading to difficulties in labor and at times requiring Cesarean Section.

It may be pointed out that actually instead of producing the desired effects (an abortion), potassium permanganate causes trauma, serious injury to the vaginal walls, ulceration in the vagina, massive vaginal hemorrhage and, quite often, a secondary infection.

The massive hemorrhage produced by the corrosive action of the chemical leads to the erroneous notion that it is an effective drug in terminating pregnancies. The drug, as a matter of fact, instead of being an effective abortifacient, is a strong oxidizing agent, highly caustic and causing great tissue destruction. It should therefore not be used for internal medication except for topical application and only in concentrations not exceeding .04% aqueous solution of potassium permanganate.

In an inquiry to Dr. Milton Helpert, the Chief Medical Examiner of the City of New York, relating to fatalities from potassium permanganate in abortions, his office reports that seldom if ever is this found as a cause of death because the severe bleeding causes the patient to get medical attention. In view of the Chief Medical Examiner's comment, it is hoped that patients will not now have recourse to more dangerous over-the-counter products since potassium permanganate has recently been made a prescription item.

#### TOXICOLOGY

Oral potassium permanganate poisonings chiefly result from either accidental ingestions or suicidal attempts. The clinical manifestations vary with the dose ingested and the concentration.

In low or moderate concentrations, 1% solutions, the usual symptoms are burning in the throat, nausea, vomiting, moderate gastroenteritis, and some difficulty in swallowing, with no systemic manifestations. In higher concentrations, i.e., 2-3% solutions, in addition to the above symptoms, the patient also appears anemic, the pharynx becomes edematous and the patient may experience difficulty in swallowing and speaking. There is a dryness of the mucous membranes of the mouth due to the tanning by potassium permanganate; the patient also has difficulty in salivation. In severe cases, 4-5% solutions, there may be kidney involvement associated with albuminuria. Salivation may be either excessive or become entirely suppressed and the salivary glands become edematous due to the reduction of saliva. In addition to the gastroenteritis, in severe cases, the stools may become bloody and the patient may also present a picture of circulatory collapse with low blood pressure, rapid and shallow pulse. At times, these symptoms may be accompanied by paresthesias and disorientation. If death occurs, it is usually due to circulatory failure or pulmonary complications.

The treatment of potassium permanganate poisoning includes gastric lavage, copious amounts of fluid, careful observation and supportive therapy. Milk and dilute alcohol solution are suggested to provide oxidizable organic material.

Since potassium permanganate is such a widely used product and is a strong oxidizing agent and chemically highly caustic and tissue-destroying, it is believed by medical authorities that the only dosage form of potassium permanganate which may be judged to be safe for use in self-medication are aqueous solutions which contain not more than 0.04% of potassium permanganate. Such solutions are believed to be safe for use and only for external application to the skin.

Recently, the United States Food and Drug Administration took the necessary action to make this potentially toxic agent a prescription item and provided that all such preparations will be regarded as misbranded if at any time prior to dispensing, the label fails to bear the legend: "Caution—Federal law prohibits dispensing without prescription".<sup>2</sup>

While the action by the United States Food and Drug Administration is to be commended, it is not sufficient to prevent serious accidental potassium permanganate poisonings. Since the prep-

aration will still be accessible in the home, regardless how obtained, it is still a potential hazard, either from accidental ingestion or from misuse. When prescribing or dispensing potassium permanganate, physicians must alert women on the hazards associated with its misuse as a vaginal douche or abortifacient, and they must also caution the adults in the family to keep this product securely locked and away from children.

The following list relating to incidents reported to the Poison Control Center during a recent weekend illustrates the extent of the poisoning problem in New York City.

Product Ingested	Age of Patient§	Sex
Alcohol, rubbing	2	M
Ammonium hydroxide	30	F
Amytal	55	M
"Ant Trap" (Insecticide)	2	F
Aspirin	2	M
Aspirin	5	F
Aspirin (possibly 26 tablets)	2½	M
Barbiturate	22	F
Barbiturate (fatal)	64	F
Bellergal (Anti-spasmodic)	1	M
Bisodol (Anti-acid)	3	F
Bleach ("Dip-It")	—	F
Boric Acid	22	F
Boric Acid	75	F
Calgonite	10 m.	F
Camphorated Oil	4 m.	M
Carbena Cleaning Fluid and Witch Hazel	17	F
Cement, plastic ("Boxer")	3	F
Christmas Ornament Ball	1½	F
Cigarettes	17 m.	M
Clorox (Bleach)	4	M
Compazine (Tranquilizer)	35	M
Cough Syrup	3	M
Crayons	18 m.	F
Deodorant ("Roll-on")	2	M
Deodorant (Diaper pail)	15 m.	M
Deodorant (Spray)	3	M
Detergent	1	M
Dexedrine and Dexamyd	4	M
Floor Wax ("Preen")	2	F
Hair Color	42	M
Hair Spray (in eyes)	—	F
Hair Spray	13	F
Ink ("Sanford's" Green)	2	M
Ink ("Speedball" White)	2	F
Insect Spray	17	M
Insect Spray	2	M
Lestoil (Detergent)	57	F
Liniment ("Sloan's")	26	M
Liniment	21 m.	F
Lubricating Oil	20 m.	M
Lye	1	M
Lye	24	M

Product Ingested	Age of Patient§	Sex
Mercury (Thermometer)	16	M
Merthiolate	40	F
Mineral Spirits	2	M
Mr. Clean (Detergent)	6	F
Narcotic (fatal)	25	M
Noludar (Tranquilizer)	21	F
Nytol (Sleeping pill)—Methapyrilene	—	F
Oil, altar	3	M
Oil of Cloves	4	M
Paint (Bit on tube)	2	M
Paste (Lassar's)	1½	F
Perfume	19 m.	M
Perfume	18 m.	M
Phenobarbital	17	F
Phenergan (Anti-histamine)	36	F
Potassium Permanganate	—	M
Potassium Permanganate	2	F
Rodenticide powder	18	F
Seconal	—	F
Shoe Polish ("Esquire Scuff Coat")	2	F
Sleeping Pills	49	F
Snow, artificial	17 m.	F
Sominex (Sleeping pill)—Methapyrilene	30	F
Sparine (Tranquilizer)	26	F
Sparine ( )	42	M
Sulphur and "Flit" (Insecticide)	20	F
Thermometer	1	F
Turpentine	18 m.	F
Unknown Drug	4½	F
Unknown Drug	1	M
Unknown Drug (possible contact allergy)	41	M

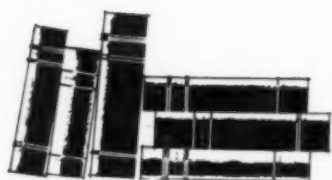
§In years unless months (m.) is indicated

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2. "Federal Register", Vol. 25, No. 164, p. 8073, Aug. 23, 1960.

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(This is the fifth of a series of papers by Dr. Jacobziner)



... Books

Edited by

MICHAEL A. BRESCIA, M.D.

RESUSCITATION OF THE NEWBORN INFANT. Edited by Harold Abramson, M.D. Cloth. Illustrated. Pages 274. The C. V. Mosby Company, St. Louis 1960. \$10.00.

Dr. Abramson has produced an excellent and valuable work which should contribute materially in improving resuscitative techniques. Twenty-three contributors in addition to the editor are responsible for this important work. All of the authors are members of the Special Committee on Infant Mortality of the Medical Society of the County of New York. The authors do not confine themselves merely to the actual resuscitative process, important though it be, but as the editor states in his preface, the book "encompasses the investigation, early recognition, and appraisal of all influences operating before conception, during pregnancy, in and around the birth of the baby, and immediately after birth which may possibly contribute to perinatal distress, thus making necessary early institution of preventive measures or prompt application of well-conceived procedures to revive the infant should respiratory failure occur".

The second chapter on Physiology and Biochemistry is especially good. However, this reviewer thought that a little more discussion and weight should have been given to Jaykka's theory that normal lung expansion is related to high pulmonary arterial pressure. His experiments which lead him to his conclusion would have been worthwhile if they had been reproduced.

The first sixty seconds of life are the most important and most precarious of entire life and appropriately there is a chapter so named. This most important chapter seems to be more equivocal than authoritative. This is only a minor criticism. The chapter and book as a whole have great merit.

Many procedures are adhered to not because of any rational reason but by custom and lack of something better to do. Hence, it was salutary to note in the chapter on Drug Therapy the authors' suggestion that "probably the only agent necessary in the delivery room is oxygen". They also advise against the indiscriminate use of so-called respiratory stimulants since "they may in fact deepen the depression by increasing the oxygen requirements of the brain cells".

This book is invaluable to obstetricians, pediatricians and anesthesiologists and should certainly be in every hospital library. M.A.B.

THE METABOLIC BASIS OF INHERITED DISEASE. Edited by John B. Stanbury, M.D., James B. Wyngaarden, M.D., and Donald S. Fredrickson, M.D. Blakiston, McGraw-Hill Book Co., Inc. 1960. \$30.

In 1909, Sir Archibald Garrod published a monograph entitled "Inborn Errors of Metabolism" in which he described his observations on four entities; alcaptonuria, cystinuria, albinism, and pentosuria.

Stanbury, Wyngaarden, and Fredrickson have now edited a 1477 page book, written by 47 contributors summarizing the existing biochemical and genetic knowledge of over 100 diseases due to an "inborn error of metabolism". Most of this information has been accumulated in the last decade, and since knowledge of these disorders is accumulating so rapidly, parts of this book are already out of date.

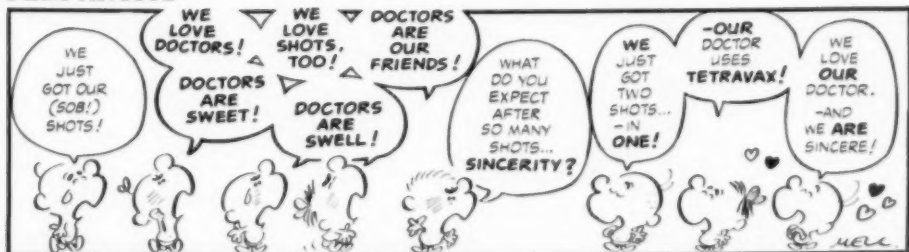
Since these diseases are inherited and usually become manifest in the pediatric age group, they should be of primary concern to the pediatrician. And since they are so rare, diagnosis is usually difficult. For these reasons this book is recommended for careful study, in spite of the fact that it probably will not become dog-eared from constant reference in a busy pediatrician's office.

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